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Office of Vermont Health Access

HMG-CoA Reductase Inhibitors and HMG-CoA Reductase Inhibitor/Ezetimibe Combination Update

Overview

Hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly known as "statins") work by inhibiting HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in an early step in the biosynthetic pathway for cholesterol. This inhibition decreases cholesterol synthesis causing an up-regulation of hepatic low-density lipoprotein (LDL) cholesterol receptors and enhanced clearance of circulating LDL cholesterol (LDL-C).

Lowering total cholesterol and LDL-C and raising high-density lipoprotein cholesterol (HDL-C) are important goals as deposition of cholesterol in the arterial walls is central to the pathogenesis of atherosclerosis in the coronary arteries. A direct correlation exists between total cholesterol, LDL-C, and the risk of developing coronary heart disease (CHD), while an indirect correlation exists between HDL-C and the risk of developing CHD.[1] HMG-CoA reductase inhibitors are the most potent LDL-C lowering agents with LDL-C reductions ranging from 20-60%. These agents also have the ability to moderately raise HDL-C. In addition, HMG-CoA reductase inhibitors have demonstrated reductions in cardiovascular morbidity and mortality.

Ezetimibe (available as Zetia® or in combination with simvastatin as Vytorin®) reduces cholesterol levels by inhibiting its absorption by the small intestine, resulting in decreased hepatic delivery and storage and an increased clearance of cholesterol from the blood. It reduces LDL-C by approximately 18% and can cause small increases in HDL-C. This mechanism of action complements the action that exists with statins, allowing it to be used either as monotherapy or as adjunctive therapy to statins.

Ezetimibe/simvastatin (Vytorin®) is approved by the FDA as an adjunct therapy to diet for the reduction of total cholesterol, LDL-C, Apo B, triglycerides and non-HDL-C and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia; as well as an adjunct to other lipid-lowering treatments to reduce total cholesterol and LDL-C in patients with homozygous familial hypercholesterolemia.[2] In contrast, the single entity statin products do have expanded indications, including: primary dysbetalipoproteinemia, homozygous familial hypercholesterolemia, hypertriglyceridemia, heterozygous familial hypercholesterolemia in adolescent patients, primary prevention of CHD, primary prevention of coronary heart disease in patients with type 2 diabetes, secondary prevention of coronary heart disease, slowing the progression of coronary atherosclerosis in CHD, and reducing the risk of mortality from CHD. To date, very limited data have been published demonstrating the effect of ezetimibe/simvastatin on cardiovascular events, and no incremental benefit of ezetimibe/simvastatin on cardiovascular morbidity and mortality over that demonstrated by simvastatin has been established. As such, ezetimibe and ezetimibe/simvastatin are not recommended as initial treatment of hypercholesterolemia.

National guidelines for the treatment of high cholesterol, including the third report of the Expert Panel on Detection, Evaluation and Treatment in Adults (ATP III), consider HMG-CoA reductase inhibitors the initial drugs of choice for monotherapy for primary and secondary prevention of cardiovascular disease.[3,4]

Efficacy

Clinical trials have shown that the lipid-lowering efficacy and overall safety of the combination product Vytorin® is similar to simvastatin and ezetimibe when administered as separate agents. The ENHANCE clinical trial (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) was conducted comparing ezetimibe 10 mg and simvastatin 80 mg versus simvastatin 80 mg alone in reversing the atherosclerotic thickening of the carotid artery in patients with heterozygous familial hypercholesterolemia.[5] Although studies have shown that the combination of ezetimibe and a statin is more efficacious in improving lipid parameters than monotherapy with either agent, the recently published results of the ENHANCE trial did not show

that these reductions led to a significant reduction in atherosclerosis progression. The SEAS clinical trial (Simvastatin and Ezetimibe in Aortic Stenosis) was recently published and compared ezetimibe 10 mg and simvastatin 40 mg with placebo in patients with mild-moderate, asymptomatic aortic stenosis.[6] This study concluded that the combination therapy did not reduce the composite combined outcome of aortic valve events and ischemic events. While it was found to have a reduction in the incidence of ischemic cardiovascular events, there was no clinical benefit related to aortic valve stenosis events.

JUPITER was a large, double-blind, placebo-controlled, multicenter, landmark trial evaluating the role of rosuvastatin 20 mg daily and placebo for primary prevention of cardiovascular events in patients with normal LDL-C but elevated C-reactive protein levels.[7] JUPITER was designed as a four-year trial but was stopped prematurely after a median of 1.9 years of follow up due to significant cardiovascular morbidity and mortality benefits observed in the rosuvastatin group. While the incidence of serious adverse effects was comparable in the two groups, more rosuvastatin-treated patients developed new diabetes and had higher glycated hemoglobin levels. Moreover, this study was not designed to establish the role of C-reactive protein in determining the need for rosuvastatin therapy.[7,8] Therefore it is not clear from the results of this study whether the significant benefit in vascular outcomes noted with rosuvastatin therapy was a consequence of its LDL-C lowering effect, C-reactive protein reduction, or both.

ENHANCE trial:
The ENHANCE trial consisted of 720 patients with familial hypercholesterolemia with a primary endpoint of mean change in the intima-media thickness (IMT) measured at three sites in the carotid artery. No significant difference was found in this primary endpoint between the treatment groups (ezetimibe-simvastatin 10/80 mg compared to patients treated with simvastatin 80 mg alone) during the 24-month study period. The mean change in the carotid artery IMT from baseline was 0.0111±0.0038 mm in the ezetimibe-simvastatin group and 0.0058±0.0037 mm in the simvastatin monotherapy group, however the difference (0.0053 mm) did not reach statistical significance (P=0.29). The change in the average IMT did not differ significantly between the two treatment groups over time; however a slight increase in thickness over the study period was observed. The average thickness at 24 months was 0.0121±0.0038 mm in the ezetimibe-simvastatin group (P<0.01) and 0.0095±0.0040 mm in the simvastatin monotherapy group (P=0.02).

Secondary outcome measurements did not yield any statistically significant benefits in outcomes. There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (45.3% vs. 44.4%; P=0.92) or new plaque formation (4.7% vs. 2.8%; P=0.20) receiving ezetimibe-simvastatin and simvastatin monotherapy, respectively. Also reported, there was no significant change from baseline in the mean maximum carotid artery IMT (0.0175±0.0049 mm and 0.0103±0.0049 mm, respectively; P=0.27). No significant changes were observed between study groups regarding mean thickness measurements of the common carotid artery (P=0.93), carotid bulb (P=0.37), internal carotid artery (P=0.21) and femoral artery (P=0.16) or average of the mean values for carotid and femoral artery IMT (P=0.15).

After 24 months of treatment, mean LDL-C decreased by 55.6 mg/dL in the combination group and by 39.1 mg/dL in the simvastatin group, resulting in a between-group difference of 16.5% (P<0.01). The reduction in triglycerides at 24-months illustrated a between-group difference of 6.6% (P<0.01), and a C-reactive protein between-group difference of 25.7% (P<0.01), both of which were significantly higher with simvastatin-ezetimibe combination therapy vs. simvastatin alone. Combination therapy also resulted in a greater LDL-C reduction (between group difference of 16.5%) compared to simvastatin alone.

SEAS Trial:
The SEAS trial consisted of 1,873 patients with mild-moderate aortic valve stenosis with primary endpoints of major cardiovascular events, a composite consisting of death from cardiovascular causes, aortic-valve replacement, congestive heart failure as a result of progression of aortic-valve stenosis, nonfatal myocardial infarction, hospitalization for unstable angina, coronary-artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or non-hemorrhagic stroke.[6] This outcome included aortic valve-related clinical events and ischemic events to account for possible cardiovascular symptoms and events occurring in patients with aortic-valve stenosis. The major secondary outcomes included aortic valve events (need for valve replacement, CHF

due to aortic stenosis, or death from cardiovascular causes), ischemic events including cardiovascular deaths, non-fatal myocardial infarctions, unstable angina hospitalizations, CABG, PCI, and non-hemorrhagic strokes, as well as progression of aortic stenosis. The primary composite outcome occurred in 35.3% (n=333) of patients in the simvastatin–ezetimibe group and 38.2% (n=355) of patients in the placebo group, resulting in a hazard ratio (HR) of 0.96 (95% CI, 0.83 to 1.12; *P*=0.59). The only composite component reaching statistical significance was the need for CABG, which occurred more often in the placebo group (10.8%) compared to the ezetimibe-simvastatin group (7.3%), resulting in a HR of 0.68 (95% CI, 0.50 to 0.93; *P*=0.02).

None of the secondary outcomes of aortic valve-related events, including aortic valve replacement, death from cardiovascular causes, and hospitalization for CHF due to stenosis progression was shown to be significantly different in the two treatment groups, yielding a HR of 0.97 (95% CI, 0.83 to 1.14; *P*=0.73). The composite secondary outcome related to ischemic events favored the ezetimibe-simvastatin group over the placebo group, with 15.7% of active treatment patients experiencing an event compared to 20.1% of placebo patients [HR: 0.78, 95% CI, 0.63 to 0.97; P=0.02). The specific composite components of nonfatal myocardial infarction, PCI, hospitalizations for unstable angina, non-hemorrhagic stroke, and death from cardiovascular causes did not show a statistically significant difference between treatment groups. Aortic valve replacement was necessary in 267 (28.3%) of ezetimibe-simvastatin patients and 278 (29.9%) of placebo patients, yielding a HR of 1.00 (95% CI, 0.84 to 1.18; *P*=0.97). Of note, there was a significant reduction in the need for CABG intervention. A total of 69 patients in the active treatment group (7.3%) compared to the 100 placebo-treated patients (10.8%) required the intervention, resulting in a HR of 0.68 (95% CI, 0.50 to 0.93; *P*=0.02).

Similar mean peak aortic jet velocities (±SD), the predefined echocardiographic measure for the evaluation of aortic stenosis progression, were seen in both treatment groups. The mean peak aortic jet velocity was 3.69±0.78 m/sec at endpoint, an increase of 0.61±0.59 m/sec in the ezetimibe-simvastatin group as compared to 3.71±0.76 m/sec at endpoint, an increase of 0.62±0.61 m/sec in the placebo group, indicating a lack of clinical significance between the two groups. Additionally, annualized changes in the mean peak aortic-jet velocity were 0.15±0.01 m/sec per year in the simvastatin-ezetimibe group and .16±0.01 m/sec per year in the placebo group.

Overall, there was no significant difference in overall mortality among the two treatment groups. Non-cardiovascular causes of death did occur more often in the active treatment group (5.9%) vs. the placebo group (4.7%), yielding a HR of 1.26 (95% CI, 0.85 to 1.86; *P*=0.26). The adverse events reporting was similar across the treatment groups, however cancer reports were higher among the ezetimibe-simvastatin group. Incident cancer was diagnosed in 105 patients (11.1%) in the ezetimibe-simvastatin group, as compared with 70 patients (7.5%) in the placebo group (*P*=0.01). Further evaluation is necessary to definitively link cancer with ezetimibe/simvastatin therapy especially since some cancers were diagnosed in the preceding trial, and fatal cancer incidence numbers included recurrent cancers.

JUPITER trial:
The JUPITER trial consisted of 17,802 men (50 years and older) and women (60 years and older) without a history of cardiovascular disease and a baseline LDL-C level less than 130 mg/dL.[7] All patients underwent a 4-week, placebo, run-in period during which medication adherence was assessed. Patients demonstrating adherence of at least 80% were subsequently randomized to receive either rosuvastatin 20 mg daily or placebo therapy. The primary outcome was occurrence of the first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. Secondary outcome measures included individual components of the primary endpoint. The median duration of follow-up was 1.9 years. A significantly greater percentage of patients in the placebo group experienced the primary endpoint compared to patients receiving rosuvastatin therapy (2.8% vs. 1.6%; HR, 0.56; 95%CI, 0.46-0.69; *P*<0.00001). According to the study authors, 95 patients would need to be treated with rosuvastatin for two years to prevent one primary endpoint. Moreover, treating 25 patients with rosuvastatin for 5 years was estimated to prevent one primary endpoint. In perspective, rosuvastatin therapy was associated with an absolute reduction in the risk for experiencing the primary endpoint of 1.2%.

In addition, rosuvastatin therapy was associated with statistically significant benefits in all the secondary outcomes, except for hospitalization for unstable angina. A significantly greater number of patients in the placebo

group vs. rosuvastatin experienced a nonfatal myocardial infarction (62 vs. 22; HR, 0.35; 95%CI, 0.22-0.58; *P*<0.00001) and any myocardial infarction (68 vs. 31; HR, 0.46; 95%CI, 0.30-0.70; *P*=0.0002). In addition, placebo-treated patients were associated with a greater risk for nonfatal stroke (58 vs. 30; HR, 0.52; 95%CI, 0.33-0.80; *P*=0.003) and any stroke (64 vs. 33; HR, 0.52; 95%CI, 0.34-0.79; *P*=0.002) compared to the rosuvastatin group. Nonfatal arterial revascularization (131 vs. 71; HR, 0.54; 95%CI, 0.41-0.72; *P*<0.0001) and a composite endpoint of arterial revascularization or hospitalization for unstable angina (143 vs. 76; HR, 0.53; 95%CI, 0.40-0.70; *P*<0.00001) occurred more frequently in the placebo group vs. rosuvastatin group. A significantly greater number of patients in the placebo group experienced a composite endpoint of myocardial infarction, stroke, or confirmed death from cardiovascular causes vs. patients receiving rosuvastatin therapy (157 vs. 83; HR, 0.53; 95%CI, 0.40-0.69; *P*<0.00001). The incidence of reported serious adverse effects was similar between the two groups (*P*=0.60). However, a significantly greater number of patients receiving rosuvastatin therapy developed new diabetes compared to placebo (270 vs. 216; *P*=0.01). Rosuvastatin therapy was also associated with a marginally higher median glycated hemoglobin level at 24 month vs. placebo (5.9% vs. 5.8%; *P*=0.001).

At baseline, the median LDL-C and HDL-C levels were 108 mg/dL and 49 mg/dL in both groups, respectively. The C-reactive protein level was 4.2 and 4.3 mg/L in the rosuvastatin and placebo groups, respectively. After 48 months of treatment, median LDL-C decreased by 53 mg/dL in the treatment group and increased by 1 mg/dL in the placebo group, resulting in a between-group difference of 50% (*P*<0.001). The reduction in C-reactive protein at 48-months culminated in a between-group difference of 34% (*P*<0.001), and a triglycerides between-group difference of 16.1% (*P*<0.001), both of which were significantly higher with rosuvastatin vs. placebo. There was no statistically significant change in the HDL-C level from baseline, with both groups exhibiting an increase of 1 mg/dL.

American Heart Association (AHA) Comment on the JUPITER Trial [8]**:**
The release of the JUPITER trial, published online in the New England Journal of Medicine on November 9, 2008, coincided with the American Heart Association (AHA) 2008 Scientific Session. AHA guidelines have long recognized the benefit of cholesterol reduction in secondary and primary prevention of patients at increased risk for coronary disease. The JUPITER trial demonstrated significant reductions in cardiovascular events among patients with normal baseline LDL-C levels treated with rosuvastatin for a median of two years, suggesting a potential new role for statin therapy. However, the president of the ACC noted that JUPITER was not designed to assess whether the observed reduction in cardiovascular risk was due to the LDL-lowering effect of rosuvastatin or its anti-inflammatory activity, marked by a reduction in C-reactive protein level from baseline. To date, no formal statements or guideline updates have been issued by the AHA or any other national organization in response to the JUPITER trial.

American College of Cardiology (ACC) Statement on the ENHANCE Trial [9]**:**
The ACC released a statement on January 15, 2008 in response to media reports on the results of the ENHANCE trial. Designed to prove that ezetimibe-simvastatin combination therapy would slow the growth of plaque in the carotid arteries more than simvastatin alone, the ACC notes the lack of benefit in terms of affecting the rate of atherosclerosis progression. However, they recommend that major clinical decisions should not be made on the basis of this trial alone.

The ACC also notes the lack of urgency of this situation and emphasizes that further research is necessary to provide conclusive evidence regarding the use of statin monotherapy or combination therapy with ezetimibe. Furthermore, the ACC highlights that this was an imaging study and not a clinical outcomes study, adding to their emphasis that significant decisions should not rest solely upon this study.

The ACC does continue to recommend that Zetia® remains a reasonable option for patients currently on high-dose statin therapy who are yet to achieve lipid-lowering goals, as well as for those unable to tolerate statins (or can only tolerate a low dose of statins). The ACC standpoint includes not drawing therapy conclusions regarding ezetimibe and ezetimibe combination products until large, outcome trials have been conducted (anticipated results within 2-3 years).

Additional Information[10]:
According to an article in the Wall Street Journal, federal and state prosecutors are investigating the marketing practices of Vytorin® and The Department of Justice is specifically attempting to establish whether the company's promotion of the product prompted false reimbursement claims to be made to healthcare programs regulated by federal funding.[10] Earlier this year, The House Energy and Commerce Committee began vigorously investigating the marketing and safety of Vytorin®. Their belief is that "real and serious issues may have affected consumer pocketbooks, if not their health." Merck has also been accused of delaying the results of the ENHANCE trial to protect sales which, once published, illustrated that the more expensive Vytorin® product was not better than the cheaper generic, simvastatin product.

Recommendations
HMG-CoA Reductase Inhibitors are recognized as primary therapy for cholesterol reduction and reduction in cardiovascular morbidity and mortality. In addition, ezetimibe in combination with a statin is currently recognized as a treatment option in patients unable to achieve or sustain target LDL levels on a statin alone. Despite the potential of recent evidence to impact future consensus guideline recommendations, no guideline updates have been issued to date. Due to uncertain implications of the new data described above, no changes are recommended to the current approval criteria at this time.

Crestor® is preferred on The Office of Vermont Health Access (OVHA) preferred drug list and is available without a prior authorization after a documented side effect, allergy, or treatment failure to generic simvastatin.

Zetia® requires prior authorization with the following approval criteria:
- The patient has a documented side effect, allergy or contraindication (eg. drug interaction) to a statin.

OR
- The patient has a diagnosis of homozygous sitosterolemia.

OR
- The patient has had an inadequate response to BOTH generic simvastatin and Crestor®

AND
- The quantity requested does not exceed 1 tablet per day.

Vytorin® requires prior authorization with the following approval criteria:
- The patient has had an inadequate response to both generic simvastatin and Crestor®.

Characteristics of the Statins & Ezetimibe Products[11-20]

	Lovastatin (*Mevacor*)	**Pravastatin (*Pravachol*)**	**Simvastatin (*Zocor*)**	**Fluvastatin (*Lescol*)**	**Atorvastatin (*Lipitor*)**	**Rosuvastatin (*Crestor*)**	***Ezetimibe (Zetia)***	***Vytorin (simvastatin/ ezetimibe)***
Average Decrease in LDL-C	20 mg: 29% 40 mg: 31% 80 mg: 40%-48%	10 mg: 19% 20 mg: 24% 40 mg: 34% 80 mg: 40%	10 mg: 28% 20 mg: 35% 40 mg: 40% 80 mg: 48%	20 mg: 17% 40 mg: 23% 80 mg: 33%	10 mg: 38% 20 mg: 46% 40 mg: 51% 80 mg: 54%	5 mg: 43% 10 mg: 50% 20 mg: 53% 40 mg: 62%	10 mg: 18%	10/10mg - 80/10mg 45-60%
Increase in HDL-C	2-9%	2-12%	8-16%	3-9%	5-9%	3-17%	1%	6-8%
Decrease in TG	6-27%	11-24%	12-33%	12-23%	19-37%	45-60%	7-9%	23-31%
Renal Function	Use lower doses for severe renal impairment.	Use lower doses for severe renal impairment.	Use lower doses for severe renal impairment.	No dose adjustment necessary for reduced renal function.	No dose adjustment necessary for reduced renal function.	Use lower doses for severe renal impairment.	No dose adjustment necessary in renal impairment.	Use lower doses for severe renal impairment.
Solubility	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	-
Drug Interactions	Metabolized by CYP3A4 enzyme system	Not significantly metabolized by cytochrome P450	Metabolized by CYP3A4 enzyme system	Metabolized primarily by CYP2C9 enzyme system	Metabolized by CYP3A4 enzyme system, but less than lovastatin and simvastatin	Limited CYP450 2C9 metabolism	Not metabolized by cytochrome P450	Metabolized by CYP3A4 enzyme system (simvastatin)

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